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Jerry D. Frantz, V.M.D.
Vice President
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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0389; *Draft Guidance for Industry on Nonclinical Studies for Development of Pharmaceutical Excipients, 67 Federal Register 61910 (October 2, 2002)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated $2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance for Industry on Nonclinical Studies for Development of Pharmaceutical Excipients. We commend the FDA for providing this draft guidance on nonclinical studies for the development of pharmaceutical excipients. We begin with general comments followed by more specific concerns with the proposal.

Summary of BMS Comments on Proposal

With this guidance, the FDA is proposing a testing paradigm for the nonclinical studies for the development of pharmaceutical excipients. In our view, there are several aspects of the draft document that require additional clarity and specific recommendations, and the inclusion of greater flexibility in the evaluation paradigm. We would also encourage the Agency to publish a list of currently acceptable excipients. Our comments and suggestions are intended to provide feedback to the Agency so as to enhance the understanding of intent, and not to discourage the development of new excipients.

The current draft dictates a similar, high level evaluation for all excipients, without taking into account differences in the specific characteristics of the excipient(s), including broad parameters, such as biological behavior (active versus inert), bioavailability or the toxicokinetic profile. The current draft should provide an avenue for a more limited scope of testing based on scientific evaluation of the characteristics of the excipient. For example, it would seem appropriate for the

Agency to have differing expectations and establish a multi-tiered guidance that would trigger a unique, limited evaluation when no systemic effects are observed following a reduced number of scientifically valid, nonclinical studies. Also, additional clarity as to the appropriate maximum dose to be used in preclinical studies supporting new excipients would be helpful.

We would request that the Agency provide further guidance as to accessibility of excipient data from both a regulatory and industry perspective. The Agency should publish in the public domain an updated list of currently acceptable excipients, and establish a procedure by which sponsors and the public can review and retrieve submitted data on newly acceptable excipients. We would also appreciate clarification as to whether the Agency will permit the use of an excipient in a new drug product based on a similar exposure in a drug approved in another geographic location under a different regulatory authority.

The draft document recommends an extensive battery of nonclinical studies without providing guidance or recommendations on specific study design. Expanding the guidance to include these recommendations would be helpful. We would request that the Agency recommend or develop a new guidance that addresses evaluation of impurity profiles for excipients.

The current draft document does not stipulate the concentration present within a given formulation that would trigger the need for additional safety testing. The document also does not provide any guidance on the specific studies required if more than one excipient is present in the dosage form. We would encourage the Agency to utilize a paradigm similar to the one used for the qualification of impurities. This algorithm does not require the same level of testing and employs a qualification threshold based on a reasonable percentage within the dosage form.

The document deserves additional discussion regarding the appropriate maximum dose used in nonclinical studies supporting new excipients, and further interpretation as to what would be an adequate margin of safety. We would like the Agency to consider that it may not be necessary to conduct safety studies at the limit dose or maximum feasible dose (MFD). Based on precedent provided by ICH guidance, we would encourage the Agency to allow the excipient to be tested at a multiple over the intended maximum usage in humans.

Specific Comments

The current document implies that the safety database associated with a qualified excipient be brought up to current ICH standards (line 60). We ask that a grandfather clause be implemented on commonly used excipients, especially in view of the fact that these excipients have been used safely over many years. If any of these additional tests resulted in a positive finding, uncertainty would result and true relevance would need to be addressed.

Under the heading of recommended development strategies to support marketing of new excipients in drug products (Section III), the current document recommends a complete safety pharmacology battery based on ICH S7A and B guidance (line 122). We would encourage the Agency to employ flexibility based on a scientifically valid approach, and conduct the safety pharmacology battery only if significant signals were detected in an enzyme/receptor panel or

during acute nonclinical studies. We would also like to annotate that the use of non-rodents for acute studies (line 137) is not currently required by the ICH for new drug products.

We believe that the testing algorithm for developmental toxicity studies (Section III.B.5) should be philosophically similar to our suggested "triggering" approach for safety pharmacology assessment. As an example, fertility studies (line 164) would be conducted only if excipient-related adverse findings were observed in the reproductive tissues during initial comprehensive studies. Likewise, pre- and post-natal studies (line 167) would be conducted only if there were evidence of transplacental or translacteal exposure to the excipient.

With respect to chronic toxicity studies, we suggest the Agency employ more flexibility based on reasonable judgement. As a specific example, if the genetic toxicology, safety pharmacology, reproductive toxicology and 1- or 3-month toxicity testing in two species had no significant findings, we would encourage the Agency to obviate the need for additional chronic toxicity testing of the new excipient. Furthermore, should the Agency mandate chronic toxicity testing even if the excipient is not absorbed and has no relevant liabilities in safety pharmacology studies, we would encourage that the study (line 187) be conducted only in the most sensitive species.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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